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Journal

Environmental health perspectives, 108(10)

ISSN

0091-6765

Authors

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Publication Date

2000-10-01

DOI

10.1289/ehp.001081003

Peer reviewed



UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Government Laboratory Worker with Lung Cancer: Comparing Risks from Beryllium, Asbestos, and Tobacco Smoke

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Occupational medicine physicians are frequently asked to establish cancer causation in patients with both workplace and non-workplace exposures. This is especially difficult in cases involving beryllium for which the data on human carcinogenicity are limited and controversial. In this report we present the case of a 73-year-old former technician at a government research facility who was recently diagnosed with lung cancer. The patient is a former smoker who has worked with both beryllium and asbestos. He was referred to the University of California, San Francisco, Occupational and Environmental Medicine Clinic at San Francisco General Hospital for an evaluation of whether past workplace exposures may have contributed to his current disease. The goal of this paper is to provide an example of the use of data-based risk estimates to determine causation in patients with multiple exposures. To do this, we review the current knowledge of lung cancer risks in former smokers and asbestos workers, and evaluate the controversies surrounding the epidemiologic data linking beryllium and cancer. Based on this information, we estimated that the patient's risk of lung cancer from asbestos was less than his risk from tobacco smoke, whereas his risk from beryllium was approximately equal to his risk from smoking. Based on these estimates, the patient's workplace was considered a probable contributing factor to his development of lung cancer. **Key words** berylliosis, beryllium, lung neoplasms, occupational diseases, smoking. *Environ Health Perspect* 108:1003-1006 (2000). [Online 11 September 2000] <http://ehpnet1.niehs.nih.gov/docs/2000/108p1003-1006steinmaus/abstract.html>

Case Presentation

A 73 year-old-male first sought medical care for his current condition 6 months before our evaluation, when he presented to his private physician complaining of a 1-year history of cough and dyspnea. A chest X ray at that time revealed bilateral interstitial fibrosis and a left-sided pleural density. A biopsy of the left pleural density showed marked pleural fibrosis associated with a malignant neoplasm most consistent with poorly differentiated adenocarcinoma. Periodic acid-Schiff staining showed sparse intracytoplasmic mucin in the neoplastic cells, which suggested an adenocarcinoma. The surrounding lung tissue displayed focal interstitial fibrosis and numerous non-caseating granulomas. Based on the patient's history of beryllium work, a lymphocyte proliferation test was obtained and was positive for beryllium sensitization. Abdominal computed tomography (CT), brain magnetic resonance imaging (MRI), and whole-body radionuclide scans showed no evidence of an extrapulmonary primary tumor. A chest CT showed diffuse interstitial markings, a loculated pleural effusion, a tiny speculated density in the left subapical region, and mild mediastinal adenopathy.

The patient's occupational history is remarkable because he spent the majority of his working life at a single governmental research facility specializing in weapons development. He began working there in 1959 and spent the first 3 years as a maintenance mechanic, repairing and maintaining air conditioners, chillers, boilers, and other facility operations. In 1962, he began working as a chemistry technician where he frequently worked directly with beryllium. This job involved pouring and measuring beryllium oxide, growing beryllium crystals, and molding beryllium oxide into experimental nuclear reactor parts using hot presses and graphite dyes. He was also involved in both the setup and cleanup of numerous experiments using beryllium, including cleaning machinery and bagging contaminated parts. The patient worked with beryllium on almost a daily basis from 1962 until 1964, and then for a few weeks per year until 1975.

The patient stated that his work with beryllium was mostly done in a controlled environment. For example, the pouring and measuring of beryllium oxide was always done under a vacuum hood. The growing of beryllium crystals and the experiments

involving beryllium were typically performed in an enclosed box or vacuum bag. The patient also reported that when handling contaminated parts or cleaning after an experiment, he typically wore a respirator, gloves, and a lab coat. Despite these controls, the patient did not remember any strict formal decontamination procedures. He did not always immediately wash or shower after this work, and he frequently took his work clothes home. The patient also stated that although he occasionally wore a respirator, it may not have fit well because he frequently smelled fumes while wearing it.

During this same period, the patient was also exposed to asbestos. This occurred as he removed, cut, and replaced asbestos insulation used in furnaces. He did this approximately 1 or 2 hr/week; visible dust was produced during these procedures until strict controls were enforced in the early 1970s. From 1975 until 1987, the patient worked as a research technician in the tritium laboratory at the same facility, where he worked on various testing projects involving experimental nuclear reactors. He wore a radiation badge, but denied ever having "burned out" (reached acute or cumulative badge readings above the facility's allowable limits). He also denied ever being involved in any acute radiation accidents. The patient's cumulative radiation exposure was unknown, but cumulative radiation levels have been determined in other workers at this facility, and have generally been well below those associated with cancer (1,2).

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This work was supported by the University of California Center for Occupational and Environmental Health. Additional support was provided by grant 1-RO1-ESO7459-01A2 from the National Institute of Environmental Health Sciences and grant 99-00563V-10262 from the California Cancer Research Program.

Received 24 March 2000; accepted 11 July 2000.

The patient's medical history is noncontributory except that he smoked one pack of cigarettes per day from 15 to 37 years of age. He had no close family members who smoked and no other known occupational or environmental exposures to lung carcinogens such as arsenic, chloromethyl ethers, or radon.

Discussion

Estimating exposure. Based on the patient's history, the most obvious causes of his cancer seemed to be tobacco smoke, beryllium, and asbestos. We used several methods to estimate the patient's exposure and subsequent lung cancer risk for each agent. For tobacco smoke, a relatively precise assessment of exposure could be estimated because the patient was forthcoming about his past smoking history, and this history correlated well with reports in his past medical records. For beryllium and asbestos, however, personal exposure data were lacking, so less direct methods were needed to estimate the patient's exposure to these agents.

According to a verbal report from the patient's former employer, general area air levels of beryllium in the patient's work site never exceeded the threshold limit value of 2 $\mu\text{g}/\text{m}^3$. Unfortunately, the extent and accuracy of these readings is unknown. Air sampling may miss short-term, high-dose exposures, especially in areas away from the sampling device (3–5). Routine air monitoring may also miss exposures occurring during changing clothes or other decontamination procedures. Personal sampling, which would have given a clearer indication of the patient's actual exposure, was not performed.

Despite the lack of direct data, there are several indications that the patient was highly exposed. The strongest is the fact that the patient was positive for beryllium sensitization and had chronic beryllium disease (CBD). Although this disease may occur at low exposures in susceptible individuals (6), CBD is much more likely to occur in those with high exposures (6–9). Another indication that the patient was highly exposed is that his job duties were similar to those associated with high beryllium levels at other facilities. For example, airborne beryllium levels nearly 10 times the current threshold limit value were reported for metal casting in beryllium processing plants during the 1960s, the same period that our patient was most likely exposed (10,11).

Because the patient's duties involving asbestos were similar to those of asbestos insulators (i.e., the removal, cutting, and replacing of asbestos insulation), data from other sources could be used to estimate the patient's exposure to asbestos. Based on several exposure studies, Nicholson (12) estimated that average fibers counts for asbestos

insulators before the 1970s were approximately 10–15 fiber/ cm^3 (12). The similar period and comparable job duties suggest that this is a reasonable but likely high-range estimate of our patient's exposure.

Does beryllium cause cancer? The International Agency for Research on Cancer (IARC) considers beryllium definitely carcinogenic to humans (13). This classification is based primarily on two epidemiologic studies (14,15) shown in Table 1, which show small but consistent relative risks. Several earlier studies reported similar findings, but certain methodological problems limited their ability to clarify this association (16–18). In addition to the human epidemiologic data, animal studies showing consistent dose-response increases of lung tumors in rats and evidence of carcinogenicity in several other species also support the link between beryllium and cancer (13,19). Despite these data, several authors have raised doubts that a causal association between beryllium and lung cancer truly exists (20–25). These doubts are primarily a result of criticisms aimed at the human epidemiologic data. More common criticisms include the lack of direct exposure data, unclear dose-response relationships, and insufficient control of potential confounding factors such as smoking.

For example, Steenland and Ward (14) collected smoking information on only 32% of the cohort. This 32% may not represent the entire cohort, and higher than predicted rates of smoking may actually be responsible for the effects attributed to beryllium. On the other hand, the overall smoking rates estimated for the cohort were already high (61% of the cohort were estimated to be former or current smokers compared to 65% for the age-sex-adjusted U.S. population), and there is no firm evidence to suggest that smoking rates were substantially higher than this. Even if they were, the smoking rate in the cohort would have to be twice as high as that in the reference population to be responsible for a relative risk of 2.0. It is hard to imagine that the rate of smoking within the study cohort

was double that of the reference population when 65% of the reference population were current or former smokers.

Another criticism of the epidemiologic data linking beryllium to cancer is the supposed lack of clear dose-response relationships. For example, we normally expect to find a greater risk in workers who were exposed for longer periods of time, but Ward et al. (15) reported that the highest risks were found in workers with the shortest tenure. This is not necessarily inconsistent with a true dose response, however. Instead, it may be related to Ward et al.'s inclusion of both highly exposed manufacturing workers and lesser exposed administrative personnel. That is, an increased risk with shorter tenure may actually represent an increased exposure in workers with the most dusty and unpleasant jobs who were more likely to quit sooner. Unfortunately, there are no individual exposure data to confirm whether a true dose-response relationship does or does not exist.

The lack of individual exposure data has also been cited as a weakness in these studies. It should be noted that the exposure misclassification resulting from this lack of data is likely to be nondifferential. It would therefore typically bias the relative risk towards the null and not produce a spurious association (26,27). For example, the Ward et al.'s cohort included all workers in seven beryllium processing plants, so it likely included some unexposed administrative personnel (15). If this unexposed group were removed from the study, the relative risk might be greater. For example, if 30% of the cohort were unexposed administrative personnel, removing this group would increase the relative risk from 1.26 to approximately 1.40.

Although the evidence linking beryllium to cancer is somewhat controversial, dismissing beryllium as a potential carcinogen based on our current knowledge appears unwarranted, especially in light of the extensive animal data supporting this association.

Estimating risks. Because of the lack of quantifiable data, an accurate estimate of this patient's beryllium exposure is difficult to

Table 1. Selected studies of beryllium and lung cancer.

Study	Study design	Results
Steenland and Ward, 1991 (14)	For 689 people in a beryllium case registry, mortality experience in 1989 was determined and compared to U.S. rates.	Lung cancer SMR = 2.00 (95% CI, 1.33–2.89; 28 cases). For those with chronic beryllium disease, lung cancer SMR = 1.57 (95% CI, 0.75–2.89; 10 cases).
Ward et al., 1992 (15)	Cohort study of 9,225 males at seven beryllium production or processing plants.	Respiratory cancer SMR = 1.26 (95% CI, 1.12–1.42; 280 cases). With crude adjustment for smoking, SMR = 1.13. For latency > 30 years since first employment, SMR = 1.46 ($p < 0.01$; 134 cases).

Abbreviations: CI, confidence interval; SMR, standardized mortality ratio.

make. Even if his exposure could be precisely determined, the current literature provides very little dose-response data with which to make an accurate assessment of his risk. Given these limitations, the clearest indication of the patient's risks is provided by Steenland and Ward (14). This study shows that individuals with CBD had relative lung cancer mortality risks of approximately 1.5. This estimate is supported by Ward et al. (15). This study included all workers in a variety of different jobs with varied exposures to beryllium. Thus, the risks estimated from this study probably represent an average of highly exposed and minimally exposed workers. Our patient performed a variety of job duties, many of which were the same as those found in beryllium processing plants. Therefore, it could be argued that his exposures were probably similar to those of the Ward et al. cohort and that his subsequent risk of lung cancer was close to the relative risk of 1.5 which Ward et al. (15) reported for workers with latencies of over 30 years.

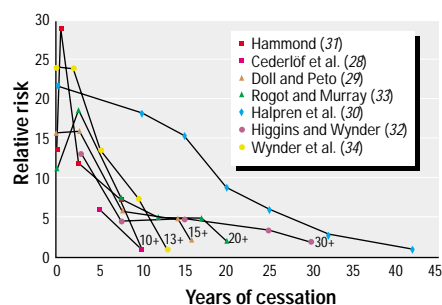


Figure 1. Studies of estimated lung cancer relative risk in former smokers (28–34). All studies presented years of cessation in broad categories. We used category midpoints for closed-ended categories to calculate mean values within these categories. In all studies except Halpren et al. (30), the category encompassing the greatest number of years of cessation was open-ended (i.e., “10+ years” since cessation). We used the lower border of the category; thus the corresponding relative risk probably represents an underestimation of the true relative risk for these data points.

Table 2. Selected results from studies of lung cancer risks in former smokers.

Study	Source	Years quit	Cigarettes/day	RR	Cases
Cederlof et al. (28)	55,000 Swedish citizens	10+	NA	1.1	3
Doll and Peto (29)	34,440 British doctors, 1951–1971	15+	9 ^a	2.0	7
Halpren et al. (30)	ACS CPS II: 852,789 people from throughout the United States, 1982–1988	40	26.4 ^a	1.08	4
Hammond (31)	ACS CPS I: 1,045,087 people in 25 states in the United States, 1959–1963	10+	20+	1.07	5
Higgins and Wynder (32)	Case control study in six U.S. cities, 2,085 male cases, 1977–1984	30+	11–20	1.8	7
Rogot and Murray (33)	248,195 U.S. Veterans, 1954–1969	20+	NA	2.10	123
Wynder et al. (34)	Case-control study in New York, 240 cases, 1966–1969	13+	NA	1.07	2

Abbreviations: ACS CPS, American Cancer Society Cancer Prevention Study; NA, not available; RR, estimated relative risk.

^aAverage for all age groups.

The patient's lung cancer risks from smoking appear to be quite similar to this estimate. As shown in Figure 1, lung cancer risks in ex-smokers tend to gradually decline as the period of cessation increases (28–34). Although current smokers can have 20- to 30-fold higher risks of lung cancer than non-smokers, relative risks may drop below 2-fold 10–40 years after quitting. Our patient had a 22 pack-year smoking history, but quit smoking 36 years ago. Table 2 provides further details on the data from Figure 1 that best reflect this smoking history. Risks in these ex-smokers range from 1.07 to 2.10. Our patient's lung cancer risk from smoking is most likely somewhere between these values, and appears essentially indistinguishable from that estimated for his beryllium exposure.

The patient's risk from asbestos seems to be lower than his risk attributable to tobacco smoke or beryllium. His exposures were probably on the order of 10–15 fibers/cm³. The patient worked with asbestos for approximately 10 years, but only for 1–2 hr/week or about 4% of his working time. Therefore, his cumulative exposure was probably near 4–6 fiber-years (10–15 fibers/cm³ × 10 years × 4% time). It was estimated that cumulative lung cancer risk increases approximately 2% for each fiber-year of exposure (35). This suggests that the patient's lung cancer risk from asbestos was near a relative risk of 1.1, and was therefore probably less than his risk from beryllium or smoking.

Conclusion

On the basis of the patient's medical and occupational history, there was strong evidence that he was exposed to relatively high levels of both beryllium and tobacco smoke. There also seems to be little solid evidence to dismiss IARC's assertion that beryllium is carcinogenic (13), although some controversy exists over the quality of the available epidemiologic data. On the basis of our review of the literature, we estimated that the patient's lung cancer risk from beryllium was roughly the same as that from his smoking. If the patient had been a current smoker or recent

ex-smoker, the patient's risk from smoking would have likely been much greater than his risk from beryllium. Because he had stopped smoking over 30 years before the diagnosis, however, we concluded that the patient's workplace experience, specifically his exposure to beryllium, was an important contributing factor to his development of lung cancer. Asbestos may have also contributed to the patient's disease, but his estimated risk from this carcinogen appears to be below that of beryllium and tobacco smoke.

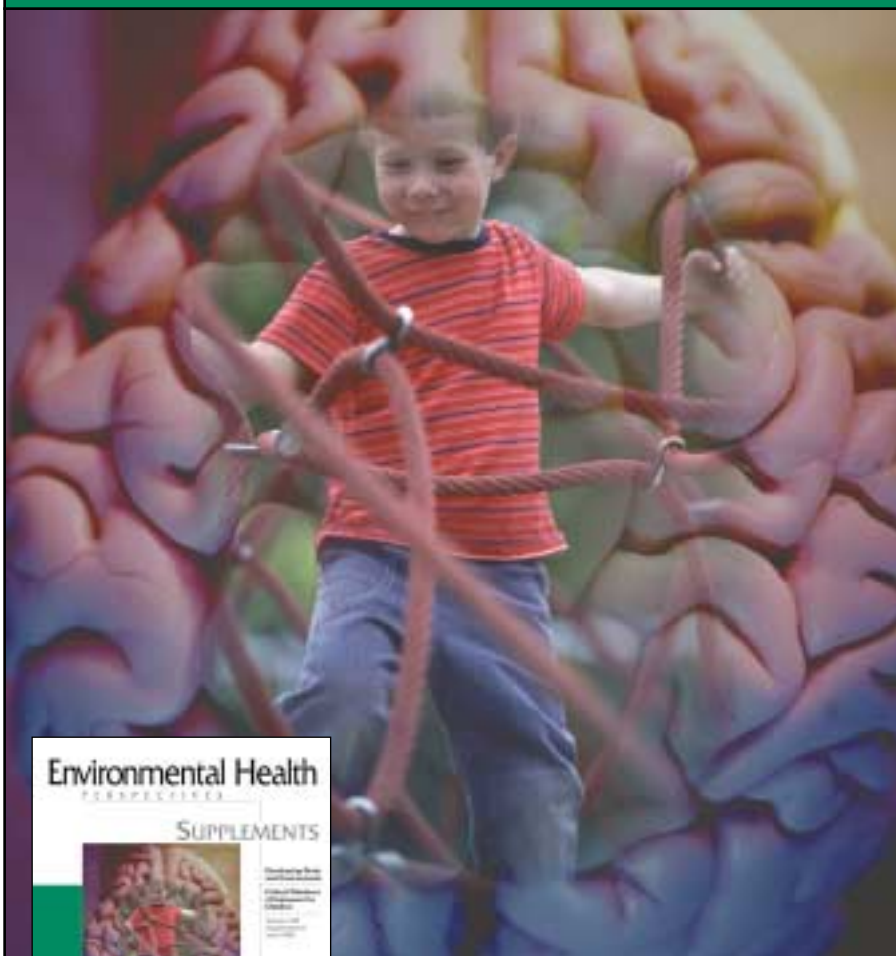
Given the limited data available, the risk estimates described in this paper are obviously inexact. Nonetheless, occupational physicians are frequently asked to provide some input on cancer causation in smokers or ex-smokers exposed to occupational carcinogens such as beryllium and asbestos. This case provides an example of the use of data-based risk estimates to determine probable causation in the common scenario of limited epidemiologic and exposure information.

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